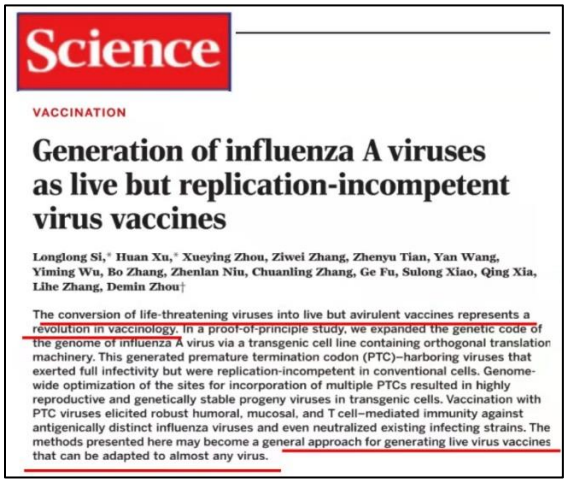
尊敬的韩少坤先生，

您好！

您发在新语丝上的一文“纵使千呼万唤周德敏，依然不见万能疫苗的影踪，造假！” 拜读，现就您提出的一些问题问题与您商榷，希望能减缓您的一些疑惑和情绪化语言。

1. 感谢您关注我们在 Science 杂志发表的“复制缺陷活流感病毒疫苗的制备”文章，不知您有没有读原文，上面清楚标注我作为通讯作者的联系方式，我一次也没有收到过您的质询，不知您“千呼万唤周德敏”何来，感谢新语丝平台否则我还真不知道您（抱歉我孤陋寡闻）。
2. 关于您质疑“这是制备活病毒疫苗的通用方法，可适用于几乎所有病毒”的结论，其实这是 Science 杂志编辑部和 Nature 等杂志评述的，是记者们根据下述的材料写出来的：


Science

VACCINATION

Generation of influenza A viruses as live but replication-incompetent virus vaccines

Longlong Si,* Huan Xu,* Xueying Zhou, Ziwei Zhang, Zhenyu Tian, Yan Wang, Yiming Wu, Bo Zhang, Zhenlan Niu, Chuanling Zhang, Ge Fu, Sulong Xiao, Qing Xia, Lihe Zhang, Demin Zhou†

The conversion of life-threatening viruses into live but avirulent vaccines represents a revolution in vaccinology. In a proof-of-principle study, we expanded the genetic code of the genome of influenza A virus via a transgenic cell line containing orthogonal translation machinery. This generated premature termination codon (PTC)–harboring viruses that exerted full infectivity but were replication-incompetent in conventional cells. Genome-wide optimization of the sites for incorporation of multiple PTCs resulted in highly reproductive and genetically stable progeny viruses in transgenic cells. Vaccination with PTC viruses elicited robust humoral, mucosal, and T cell–mediated immunity against antigenically distinct influenza viruses and even neutralized existing infecting strains. The methods presented here may become a general approach for generating live virus vaccines that can be adapted to almost any virus.

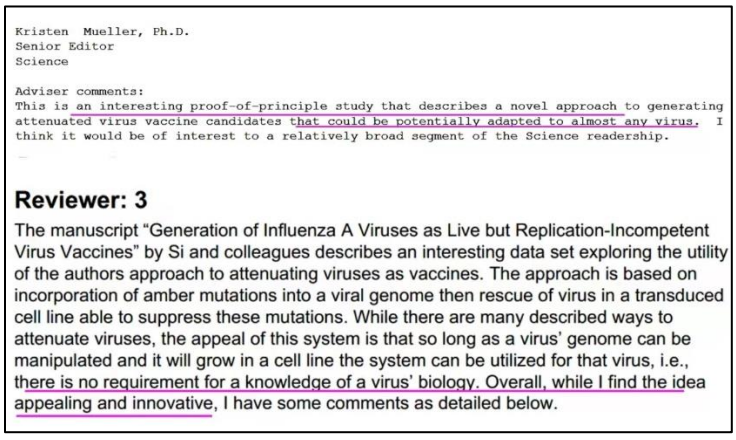

nature

New way to tame a virus

RESEARCH HIGHLIGHTS

A live, genetically modified flu virus can infect animals and trigger a strong immune response, but cannot multiply in its host's cells. Such modified viruses could one day be used to improve on current vaccines (**pictured**). Vaccines made of live viruses elicit stronger protective immune responses than inactivated vaccines, but, because they can replicate, have the potential to cause disease. To overcome this, Demin Zhou and his colleagues at Peking University in Beijing genetically altered the influenza A virus so that it could be produced efficiently by special transgenic cells, but could not replicate in normal cells or in infected animals. When compared with a commercially available inactivated flu vaccine, the modified virus stimulated stronger immune reactions in mice, ferrets and guinea pigs. Mice given the new vaccine and then infected with the unmodified flu virus survived, whereas all unvaccinated mice died.

Science 354, 1170–1173 (2016)


Kristen Mueller, Ph.D.
Senior Editor
Science

Adviser comments:
This is an interesting proof-of-principle study that describes a novel approach to generating attenuated virus vaccine candidates that could be potentially adapted to almost any virus. I think it would be of interest to a relatively broad segment of the Science readership.

Reviewer: 3

The manuscript “Generation of Influenza A Viruses as Live but Replication-Incompetent Virus Vaccines” by Si and colleagues describes an interesting data set exploring the utility of the authors approach to attenuating viruses as vaccines. The approach is based on incorporation of amber mutations into a viral genome then rescue of virus in a transduced cell line able to suppress these mutations. While there are many described ways to attenuate viruses, the appeal of this system is that so long as a virus' genome can be manipulated and it will grow in a cell line the system can be utilized for that virus, i.e., there is no requirement for a knowledge of a virus' biology. Overall, while I find the idea appealing and innovative, I have some comments as detailed below.


GEN Genetic Engineering & Biotechnology News

EXCLUSIVES NEWS THE LISTS MAGAZ

GEN News Highlights

December 2, 2016

Engineered Flu Virus a Replicative Dud, but Stays Live

Developing a live vaccine is a tricky balancing act. But it can become more of a sure thing if the vaccine developer puts a thumb on the scales. That's one way to describe the approach taken by Peking University researchers. They decided to tweak the influenza A virus genetically so that it would not only remain fully capable of activating the immune system, but would also be incapable of replicating in healthy cells.

The secret? Well, that's the proverbial thumb, which in this case is a cell line that makes use of an expanded genetic code. In cells of this line, viruses could replicate, but only in the presence of an unnatural amino acid.

Details appeared December 2 in the journal Science, in an article entitled, "Generation of Influenza A Viruses as Live but Replication-Incompetent Virus Vaccines." It described how the Peking University researchers, led by Demin Zhou, Ph.D., contrived a virus that could generate only in genetically tweaked cells, but not in healthy cells.

论文摘要的第一句和最后一句是 Science 杂志编辑的；论文发表时我没有接受过任何记者的面对面采访，只是把上述材料发给了他们。2018 年这项工作被评为“中

国科学十大进展”时，我接受过中央电视台的采访时表述过这句话，这项工作当年也被”国际疫苗学会”评为年度论文，应当是权威性。

3. 关于您提到“北京大学周德敏的万能疫苗”应该是您臆想出来的，我从来没说过造“万能疫苗”、而且科学上讲是不可能的。我研究的是制备疫苗的“通用方法”，这与“万能疫苗”完全是两个概念 - 就像现在上市的 mRNA 疫苗，是通用方法而不是万能疫苗，需要根据病毒的基因序列设计相应的 mRNA，用同样的方法来制备。 因为不了解您有否细胞生物学背景，只能解释到这个程度（很多患者当面、电话和 email 咨询我，我这样解释他们好像接受了）。
4. 所谓“周德敏在 Science 上纠正了万能疫苗的开发方法”也是您的臆想，我从未做过此事！
5. 所谓“病毒不能复制就不能感染”的结论更是您大胆的臆想！ 根据“周德敏说：以流感病毒为模型，成功研发了复制缺陷型病毒活疫苗制备技术。 该方法的核心是保留病毒完整结构和感染力,仅将病毒基因组中的一个或多个三 联遗传密码子突变为终止密码，使病毒在宿主体内的繁殖复制机制失效，同时发 挥其刺激宿主产生免疫保护的作用，甚至具有治疗前景的抗病毒药物。小鼠、雪 貂、豚鼠等动物实验表明，复制缺陷型活病毒疫苗虽然具备野生型病毒相似的感 染活性，但由于病毒复制能力缺陷，其感染之后对动物不构成生命威胁”这一段话（这是我 Science 论文的摘要翻译，很准确），是完全得不出“病毒不能复制就不能感染”这样的结论的。不过这句话反过来讲还说得过去。
6. 您提出的一系列具体科学和技术问题，比如“1、既终止密码使病毒在宿主体内的繁殖复制机制失效， 也就是复制缺陷型病毒不能在人体内繁殖，还能叫活疫苗吗？ 2、复制缺陷型病毒还具备野生型病毒的感染活性吗？病毒不能复制何来感 染”等等，其实我的 Science 论文就是在回答这些问题，如果你静下心开细细研读（前提是您要有一定的生物学背景），找到答案并不难。
7. 关于“他人无法重现周德敏的实验，在普通细胞中丧失复制能力的病毒，注射给小鼠不会扩增病毒，也就无法制备疫苗”等结论不知您是怎么得出的？其实用同样的方法做“复制缺陷型在卡病毒”两年前已在中国科学发表，用类似的方法做 HIV 假病毒、慢病毒载体、AAV 病毒也有大量论文。也请您继续关注我们的研究，最新成果也即将发表。

顺便说一下，“复制缺陷型流感病毒制备”在我们实验室已是常规实验，就像 PCR 一样，欢迎您到我们实验室亲自操作验证增长您的知识。在国家创新药物专项的支持下，“复制缺陷型流感病毒疫苗”已经处在临床前研究，几千只小鼠实验证明针对 H1N1 和 H3N2 等多种流感病毒高效，正在向禽类疫苗推进。我们在改变 293 宿主为 CHO 和 MDCK 细胞，为的是向人拓展。当然疫苗的开发需要时间，核酸疫苗有近 30 年的研发历史，希望您用科学的态度关注转化工作。

最后，给您一点建议 – 有疑问先联系我个人，如果我不答再上网不迟；否则您“千呼万唤”当事人根本不知道，只是做无用功，自己还生闷气。再一次感谢您对我研究工作的关注！也感谢新语丝提供的这个平台！

周德敏

2022，03，02